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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 13, 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,58,78-82,99 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,78-82,99 and 100* is/are rejected.

7)☒ Claim(s) *58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Upon review and reconsideration the finality of the rejection of the Office action of October 10, 2008 is withdrawn. The Amendment filed May 13, 2009 in response to the Office Action of October 10, 2008 is acknowledged and has been entered. Previously pending claims 58-64, 70, 71, 74, 83-98 have been cancelled and claims 53 and 78 have been amended. Claims 53, 58, 78-82, 99 and 100 are currently being examined.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 78-82, 99 and 100 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons previously set forth in the Office Action of October 10, 2008, section 2, pages 2-11, set forth below..

In the Office Action of December 28, 2007, section 5, pages 2-11, Examiner argued.

Applicants argue that most of the concerns raised in the action relate to the induction of a cellular immune response. One concern raised by the Action is whether the length of the various peptide fragments set forth in the claims were too long to be active in inducing a cellular immune response. In fact, professionally antigen presenting cells such as dendritic cells digest proteins into smaller peptides. In the lymph node, the DC will display these antigenic peptides on its surface by coupling them to MHC Class II molecules. This MHC:antigen complex is then recognized by T cells passing through the lymph node. Exogenous antigens are usually displayed on MHC Class II molecules, which interact with CD4+ helper T cells. CD4+ lymphocytes, or TH, are immune response mediators, and play an important role in establishing and maximizing the capabilities of the adaptive immune response. Thus, the length of a fragment is *no* bar to its suitability in generating such responses. A large fragment can be processed to provide a number of different subfragments to be presented on the surface of an Antigen Presenting Cell (see Exhibit A, pages 115 to 119 of Roitt et al., *Immunology,* 5th Edition, Mosby press, Philadelphia). Some such fragments will be of a length of sequence suitable for binding to an HLA allele. This comports with the results of Kiessling et al., already

of record, who found the presence of $CD8^+$ reactive cells which recognized two of their peptide fragments in the serum of cancer patients *who had not been administered the PSCA peptide fragments.*

Applicants arguments have been carefully considered, but have not been found persuasive because Kiessling et al. does not teach the treatment of any cancer by inducing an immune response with any of the claimed proteins and the peptides taught by Kiessling et al. are not the peptides claimed and it cannot be determined if the claimed proteins will induce an immune response that is effective to treat any of the claimed cancers because it is not known and cannot be predicted if the claimed proteins will be processed and bind MHC molecules so as to be presented in a way that will elicit an immune response that is effective for immunotherapy of cancer which is the clearly the contemplated use of the claimed method. Additionally, there is no teaching that any of the claimed peptides will interact with MHC Class II or class I molecules, which have specific constraints on are their ability to interact with a peptide, see the cited Roitt, thus it cannot be predicted that MHC class II or I will interact with the claimed proteins. Although Kiessling found $CD8^+$ reactive cells in prostate cancer patients that recognized two of their peptide fragments, the presence of these $CD8^+$ reactive cells was not sufficient to ameliorate the prostate cancer as the patients still had prostate cancer.

Applicants argue that a second concern raised in the action is the absence of clinical trials indicating any efficacy of a PSCA peptide vaccine. Thomas-Kaskel et al. have now reported the results of a clinical trial using PSCA14-22 and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), enclosed with IDS). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the setting of a "PSA relapse" after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

These results demonstrate, contrary to the Action, that the *in vitro* observations as to the PSCA peptides *are predictable* in translating to the clinic.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the specifically claimed peptides. Although new claim 98 is drawn to the method of claim 53, wherein dendritic cells are

used to present the claimed peptides to T cells in the context of MHC class I and II molecules, claim 98 depends on claim 53 where the PSCA proteins or fragments are administered to a subject directly, thus the claim does not read on administering peptide-loaded dendritic cells to a subject, but the mechanisms of presentation of the administered PSCA peptide.

Applicants argue that moreover, the very existence of such clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides:

> ... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

Applicants arguments have been carefully considered, but have not been found persuasive because, as set forth above, the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the claimed peptides.

Applicants argue that thirdly, the Examiner cites Kiessling et al. as finding that only 2 of 8 tested peptide fragments bound to the HLA-A-201. Nothing in Kiessling indicates that it took undue experimentation to identify such peptide fragments. They used standard models to identify 8 candidates and found 2 fragments to be active (i.e., PSCA14-22 and PSCA~05_113). This hardly seems to involve undue amount of experimentation. The steps performed are routine and the amount of experimentation required to identify 2 useful agents, simply *minimal* for this field of art. The standard for enablement is not whether *any* experimentation is required but whether the amount of experimentation is undue. That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands,* 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Kiessling et al. are not commensurate in scope with the claimed because Kiessling et al. do not demonstrate that any immune response to any PSCA fragment is sufficient to treat any of the claimed cancers, as set forth above.

Applicants argue that without doubt, the pharmaceutical arts are one in which it is routine to screen a large number of agents in order to find useful ones. The expenditures of substantial sums to practice an invention is no bar to enablement. Indeed, in the context of dose response,

the Federal Circuit held in 1988 that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1988).

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that previously, the Applicants cited Matsueda et al. as disclosing that one (i.e., PSCA76-84) of three tested peptides was active. Applicants now enclose with their IDS another Matsueda et al. reference which reports on the finding that two out of an additional 11 PSCA peptides (i.e., PSCA 7-15 and PSCA 21-30) were active (see, Matsueda et al., *Cancer Immunol. Immunother.* 53:479-489 (2004)). Having found them, Matsueda et al. again state that their peptides should be considered for use in clinical trials in immunotherapy. Clearly, persons of ordinary skill in the art are able to repeatedly identify suitable peptide fragments without much experimentation at all and these persons view the obtained peptides as being credible candidates for immunotherapy. The last sentence of Kiessling et al. is in accord on this last point: Our results emphasize the suitability of PSCA target molecule for the immunotherapy of prostate cancer.

Applicants' arguments have been carefully considered, but have not been found persuasive because Matsueda et al. do not use any of the claimed peptides and, although Matsueda et al. showed that two peptides elicited an immune response, Matsueda et al. did not show that the immune response was effective to treat any tumor.

Applicants argue that the invention is in the field of polypeptide vaccine development. This field of art, drug development, is traditionally one in which a large volume of screening is both typical and routine. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans.

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. Although human testing is not required, neither the specification nor the art of record has provided data that is commensurate in scope with the claimed invention so as to enable the claimed invention.

Applicants argue that as set forth in previous papers, the specification provides all the guidance required to practice the invention. Without revisiting earlier remarks, the specification discloses the PSCA protein sequence, methods of identifying CTL and antibody epitope motifs therein, and the importance of the elevation and specificity of PSCA expression in the subject

cancers. Applicants argue that with respect to inducing an immune response as in claim 78, the specification also teaches all the steps necessary to induce an immune response against a PSCA protein or fragment thereof. However, the fact that the methods were not actually practiced in subjects with cancer is no bar to enablement (see, *Brana* decision). The use of a GST-PSCA polypeptide conjugate to induce a humoral response in mice without cancer is disclosed in Example 5 at page 89 of the original specification. The epitope domains of PSCA with respect to the various monoclonal antibodies is also disclosed in the paragraph bridging pages 92 and 93.

Applicants' arguments have been carefully considered, but have not been found persuasive because in the absence of a showing that the claimed methods will induce an immune response that will treat cancer the claims are not enabled for the reasons previously set forth.

Applicants argue that, as discussed above, the state of the art is high enough for others in the field to have already begun to practice the claimed invention largely as taught by the specification (see, above discussion of the Thomas-Kaskel et al., Matsueda et al., and Kiessling et al. art).

Applicants 'arguments have been carefully considered, but have not been found persuasive for the reasons set forth above and previously.

Applicants argue that with respect to antibodies against PSCA antigen in animals with PSCA expressing cancers, Zhang et al. have confirmed that vaccination with a DNA vaccine based on human PSCA and HSP70 adjuvant enhanced the antigen-specific CD8(+) T-cell response and inhibited PSCA(+) Tumor growth in mice. (see, Zhang et al., *J Gene Med.* 9(8):715-26 (2007), enclosed with IDS).

Applicants' arguments have been carefully considered, but have not been found persuasive because the teachings of Zhang et al. are not commensurate in scope with the claimed invention as Zhang et al. is drawn to DNA vectors expressing PSCA and PSCA-HSP conjugates and are not treating with the proteins as claimed. Furthermore, it is noted Zhang et al. teaches that the PSCA alone vectors have little effect on tumor growth or survival of mice bearing PSCA expressing tumors, see figure 8, p. 723. Thus, assuming that the PSCA expressing from the DNA vector acts as a PSCA administered to a subject to elicit an immune response, as Applicants appear to be assuming, Zhang et al. demonstrates that PSCA alone is ineffective for cancer treatment.

Applicants argue that no art is without its uncertainty. However, the results achieved by Thomas-Kaskel et al., Matsueda et al., Kiessling et al., and Zhang et al. show that the uncertainties posed by the Examiner were no bar to others' practice of the Applicants' methods. In particular, as discussed above, the existence of clinical studies in and of itself is strong evidence that persons in the field consider the uncertainty in the art to be acceptably low. Applicants argue that the quantity of experimentation necessary to practice the invention with exemplified and non-exemplified aspects appears to be well within what is routinely performed by a person of ordinary skill in the art of therapeutics development. Applicants argue that as set forth in the MPEP §2164.01 (a), the final step in making the determination that "undue experimentation" would have been needed to make and use the

claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737." Considering all the above, the simple fact is *that persons in the art are using the claimed invention successfully with no sign of undue experimentation.*

Applicants' arguments have been carefully considered, but have not been found persuasive because Applicants are reiterating arguments set forth above, thus for the reasons set forth above and previously undue experimentation would be required to practice the claimed methods.

In the remarks of June 27, 2008 Applicants argued:

Applicants argue that in an earnest attempt to expedite prosecution and without acquiescing on the merits of the rejection, Applicants have amended independent claims 53 and 78 to set forth the embodiment wherein dendritic cells are used to present PSCA the protein or protein fragments to T cells in the context of MHC class I and II molecules.

Applicants argue that as outlined in Applicant's previous response, submitted on October 11, 2007 and herein incorporated by reference, the existence of clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides

... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

[underlining in the original].

Applicants argue that Thomas-Kaskel et al. (already of record) have reported the results of a clinical trial using PSCA 14-22 and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), already of record). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the setting of a "PSA relapse" after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

Applicants argue that considering the above, persons in the art are using the claimed invention successfully with no sign of undue experimentation. Thus, the claims are clearly enabled.

Applicants' arguments have been carefully considered, but have not been found persuasive. Although the teachings of Thomas-Kaskel et al. are enabling for the PSCA 14-22 peptide-loaded dendritic cells, given that the claims are drawn to numerous PSCA immunogenic fragments other than PSCA 14-22 and given the unpredictability in the art of peptide

immunotherapy and the identification of peptides that will function as claimed, undue experimentation would be required for one of skill in the art to predictably make and use the invention as claimed for the reasons previously set forth.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Applicants argue that as previously noted by the Examiner and Applicants, whether undue experimentation is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. Ex parte Forman, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The Applicants next remarks focus on those factors or concerns which were of a particular raised in the Office Action.

Applicants argue that the principal concern of the Action was the enablement of the peptide fragment subject matter of the claims. The Applicants note that the use of whole protein antigens or large fragments thereof encoding antigen(s) allows host HLA molecules to select the appropriate peptide epitope for presentation as a peptide-MHC complex on the cell surface. This approach does not require analysis of MHC molecules.

Applicants argue that accordingly, without acquiescing on the merits and in the spirit of expediting prosecution, the Applicants have amended the base claim to set forth fragments of the PSCA protein of SEQ ID NO:2 comprising amino acid residues 2 through 50 as described in SEQ ID NO:2. Accordingly, the PSCA subject matter of the base claims requires a portion of the PSCA protein which has particularly been shown to be a source of several suitable peptide

fragments which have now been shown in the art, as next discussed, to be effective in generating an immune response.

Applicants argue that in the paragraph bridging pages 10 and 11 of the Action, for instance, the Examiner acknowledged that the teachings of Thomas-Kaskel et al. were enabling for the PSCA 14-22 peptide-loaded dendritic cells. The PSCA protein and fragments of the claims embrace the Thomas-Kaskel epitope.

Applicants argue that as noted previously, the Matsueda et al. reference reported that PSCA peptides (i.e., PSCA 7-15 and PSCA 21-30) were most active (see, Matsueda et al., Cancer Immunol. Immunother. 53:479-489 (2004)) in their vaccine trials in cancer patients. Matsueda et al., recognizably with expertise in the pertinent field, conducted their experiments, as evidenced by their Abstract, with an eye to the clinical significance of their findings. They specifically concluded that their two PSCA peptides should be considered for use in clinical trials of immunotherapy of prostate cancer.

Applicants argue that with regard to the Zhang et al. reference, the Examiner was concerned that the PSCA vector (encoding the full protein) alone group did not appear to benefit from their DNA vaccines. However, it is noted that Zhang et al. also observed in the second sentence of their Abstract that DNA vaccines typically produce a less intense immune response which limits their clinical effectiveness. Hence, the need to use an adjuvant, such as HSP, given the mode of vaccination is not surprising and does not undercut the utility of the use of the full PSCA protein or its ability to be suitably processed in vivo to generate the immune response. The animals Zhang et al. treated with both the PSCA plasmid and the separate HSP plasmid did benefit from the vaccinations in terms of both tumor size and survival. Thus, the Zhang et al.

reference illustrates the ability of a DNA vaccination with the full PSCA protein to generate beneficial immune reactivity. In their research, Zhang et al. predicted and confirmed that human PSCA 28- 36 was a H-2Db-restricted epitope which is recognized by MHC I molecules in treated animals and can induce peptide specific CD8+ immune responses in C56BL/6 mice (see, for instance, the third from the last paragraph of the reference). Thus, the reference pertains in particular to an epitope within the PSCA sequence set forth in the base claims.

Applicants argue that still more recently, Ahmad S, et al. have reported (see, Molecular Therapy (2009), enclosed) their isolation of the PSCA gene from the transgenic adenocarcinoma mouse prostate cell line (TRAMPC 1) and construction of a vaccine plasmid. This plasmid PSCA (pmPSCA) was delivered by intramuscular electroporation (EP) and induced effective antitumor immune responses against subcutaneous TRAMPC 1 tumors in male C57 BL/6 mice. The pmPSCA vaccination inhibited tumor growth, resulting in cure or prolongation in survival. Similarly, the vaccine inhibited metastases in PSCA expressing B 16 F 10 tumors. There was activation of Th-1 type immunity against PSCA, indicating the breaking of tolerance to a self-antigen. This immunity was tumor specific and was transferable by adoptive transfer of splenocytes. The mice remained healthy and there was no evidence of collateral autoimmune responses in normal tissues. They concluded that EP-assisted delivery of the pmPSCA evoked strong specific responses and could, in neoadjuvant or adjuvant settings, provide a safe and effective immune control of prostate cancer, given that there is significant homology between human and mouse PSCA.

Applicants argue that as the PSCA fragment subject matter of the instant claims possess one or more suitable epitopes, the Applicants submit that persons of ordinary skill in the art can

practice the claimed invention without undue experimentation. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants have been considered, but have not been found persuasive because although SEQ ID NO: 2 or a fragment comprising amino acid residues 2 through 50 described in SEQ ID NO: 2 would predictably produce an immune response directed to a PSCA protein when loaded into dendritic cells given the showings in the post-filing reference, claims 78-82, 99 and 100 are not limited to using SEQ ID NO: 2 a fragment comprising amino acid residues 2 through 50 described in SEQ ID NO: 2 in a loaded dendritic cells. In particular, claim 78 is drawn to using "a PSCA protein of SEQ ID NO: 2", which encompasses fragments and variants of SEQ ID NO: 2 that will not predictably produce an immune response directed to SEQ ID NO: 2 that would be useful for cancer treatment given the unpredictability in the art previously set forth. Furthermore, the claims encompass cancers in non-human mammals expressing human SEQ ID NO: 2, which would not predictably be expected in the absence of genetic engineering as the different mammalian PSCA proteins have distinct amino acid sequences, see Figure 3 of the instant specification.

New Grounds of Rejection

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Examiner has established a priority date of 05/3/2000 for claims 53 and 58 because the claims as currently constituted recite "administering to the subject dendritic cells pulsed with the PSCA protein of SEQ ID NO:2 or an immunogenic fragment thereof wherein the fragment comprises amino acid residues 2 through 50 as described in SEQ ID NO:2" and a review of the parent Applications prior to application 09/564,329 does not reveal support for administering a fragment comprising the claimed limitation.

Additionally, Examiner has established a priority date of 05/14/2001for claims 78-82, 99 and 100 because 78-82, 99 and 100 claims as currently constituted recite "a method for inducing an immune response in a mammalian subject directed to a PSCA protein of SEQ ID NO:2, the subject having a cancer overexpressing a Prostate Stem Cell Antigen (PSCA) protein of SEQ ID NO:2, said cancer selected from the group consisting of prostate cancer, prostate cancer metastasized to bone, bladder cancer, and pancreatic cancer, the method comprising administering to the subject a PSCA protein of SEQ ID NO:2 or an immunogenic fragment thereof wherein the fragment comprises amino acid residues 2 through 50 as described in SEQ ID NO:2, wherein dendritic cells are used to present PSCA the protein or protein fragments to T cells in the context of MHC class I and II molecules" and a review of the parent applications

does not reveal support for performing this method in the broadly claimed mammalian subject with the fragment comprising amino acid residues 2 through 50 as described in SEQ ID NO: 2, wherein dendritic cells are used to present PSCA the protein or protein fragments to T cells in the context of MHC class I and II molecules.

Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 78-82, 99 and 100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitation in claim 81 of the method of claim 78 wherein the subject is a sheep which is encompassed by claims 78-82, 99 and 100 has no clear support in the specification and the claims as originally filed. In the remarks of June 27, 2008 Applicants pointed to support for the amended claims at page 61-lines 1 to 16 of the specification. A review of the cited support reveals:

Various ex vivo strategies may also be employed. One approach involves the use of dendritic cells to present PSCA antigen to a patient's immune system. Dendritic cells express MHC class I and II, B7 costimulator, and IL-12, and are thus highly specialized antigen presenting cells. In prostate cancer, autologous dendritic cells pulsed with peptides of the

prostate-specific membrane antigen (PSMA) are being used in a Phase I clinical trial to stimulate prostate cancer patients' immune systems (Tjoa et al., 1996, Prostate 28: 65-69; Murphy et al., 1996, Prostate 29: 371-380). Dendritic cells can be used to present PSCA peptides to T cells in the context of MHC class I and II molecules. In one embodiment, autologous dendritic cells are pulsed with PSCA peptides capable of binding to MHC molecules. In another embodiment, dendritic cells are pulsed with the complete PSCA protein. Yet another embodiment involves engineering the overexpression of the PSCA gene in dendritic cells using various implementing vectors known in the art, such as adenovirus (Arthur et al., 1997, Cancer Gene Ther. 4: 17-25), retrovirus (Henderson et al., 1996, Cancer Res. 56: 3763-3770), lentivirus, adeno-associated virus, DNA transfection (Ribas et al., 1997, Cancer Res. 57: 2865-2869), and tumor-derived RNA transfection (Ashley et al., 1997, J. Exp. Med. 186: 1177-1182).

In the remarks of June 27, 2008 Applicants pointed to support for the amended claims at page 23 of the specification, the last two full paragraphs and claim 58. A review of the cited support reveals:

Various regions of the PSCA protein can bind to anti-PSCA antibodies. The regions of the PSCA protein may include, for example, the N-terminal region, middle region, and C-terminal region (Example 18, FIG. 49). The N-terminal region includes any portion of the PSCA protein encompassed by amino acid residues 2-50, preferably residues 18-50. The middle region includes any portion of the PSCA protein encompassed by amino acid residues 46-109, preferably residues 46-98. The C-terminal region includes any portion of the PSCA protein encompassed by amino acid residues 85-123, preferably residues 85-98.

The PSCA proteins of the invention may be useful for a variety of purposes, including but not limited to their use as diagnostic and/or prognostic markers of prostate cancer, the ability to elicit the generation of antibodies, and as targets for various therapeutic modalities, as further described below. PSCA proteins may also be used to identify and isolate ligands and other agents that bind to PSCA. In the normal prostate, PSCA is expressed exclusively in a subset of basal cells, suggesting that PSCA may be used as a marker for a specific cell lineage within basal epithelium. In addition, the results herein suggest that this set of basal cells represent the target of neoplastic transformation. Accordingly for example, therapeutic strategies designed to eliminate or modulate the molecular factors responsible for transformation may be specifically directed to this population of cells via the PSCA cell surface protein

The suggested support has not been found persuasive, because there is nothing to implicitly, inherently, or explicitly suggest performing the method of claim 78 in sheep. Thus, the subject matter claimed in claims 78-82, 99 and 100 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 01/087325 (Salgaller et al. May 12, 2000).

WO 01/087325 teaches using dendritic cells load with human PSCA to treat human prostate cancer and metastatic prostate cancer, see claims 10, 14, 21, 22, 26, and 34, page 6-lines 27-32, and page 17,-lines 7-13. Although the methods of WO 01/087325 use agents that enhance MHC class I antigen presentation, the presentation of antigens in the context of MHC class II does not appear to be eliminated by such treatments.

Although the reference does not specifically state that immune response is a humoral immune response, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

6. Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,267,960 (Reiter et al. March 10, 1998).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C.

102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

USPN 6,267,960 teaches that the invention provides prostate cancer vaccines to produce humoral and cell mediated immunity. USPN 6,267,960 teaches use of dendritic cells to present PSCA antigen to a patient's immune system. Dendritic cells express MHC class I and II, B7 costimulator, and IL-12, and are thus highly specialized antigen presenting cells. In prostate cancer, autologous dendritic cells pulsed with peptides of the prostate-specific membrane antigen (PSMA) are being used in a Phase I clinical trial to stimulate prostate cancer patients' immune systems. Dendritic cells can be used to present PSCA peptides to T cells in the context of MHC class I and II molecules. In one embodiment, autologous dendritic cells are pulsed with PSCA peptides capable of binding to MHC molecules. In another embodiment, dendritic cells are pulsed with the complete PSCA protein, col. 20-line 62 to col.21-line 24.

7. Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,258,939 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,261,789 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,261,791 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,541,212 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,825,326 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,756, 036 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,881,822 (Reiter et al. March 10, 1998).

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 6,960,443 (Reiter et al. March 10, 1998),

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 7,417,113 (Reiter et al. March 10, 1998)

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 7,462,691 (Reiter et al. March 10, 1998)

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by USPN 7,527,786 (Reiter et al. March 10, 1998)

Claims 53, 78-80, 99 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat App. Pub. 2005/0026229 (Reiter et al. March 10, 1998).

The applied references have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The recited patents and application claim priority to USPN 6,267,960 filed March 10, 1998 and teach as set forth above for USPN 6,267,960.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 81 is rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,267,960 (Reiter et al. March 10, 1998) as applied to claims 53, 78-80, 99 and 100 are above, in

view of Fields et al. (PNAS USA August 1998, 95: 9482-9487), and further in view Klein et al. (Nature Medicine April 1997, 3:402- 408).

USPN 6,267,960 teaches as set forth above, but does not teach the method of claim 78, wherein the subject is a sheep, rat, dog, cat, pig, horse, or mouse. USPN 6,267,960 teaches human prostate cancer xenograft cells, LAPC-4 and 9 that express PSCA, see Example 1 and Fig. 9.

Fields et al. teach using mouse tumor models to test the effectiveness of dendritic cells pulsed with tumor lyates on inhibiting tumor growth.

Klein et al. teach generation and use of the LAPC-4 cells in immuno-deficient mice for the study of prostate tumor growth, see Abstract and Fig. 4.

It would have been *prima facie* obvious at the time the invention was made to perform the induction of an immune response with the PSCA protein and dendritic cells described by USPN 6,267,960 using the LAPC-4 xenograft model of Klein et al. to study the activity of the dendritic cells in a mouse tumor models as performed by Fields et al. because it was routine the art to examine the in vivo activity of potential cancer therapeutic agents in mouse model as performed by Fields et al. As these methods were routine in the art, one of skill in the art would have a reasonable expectation of success making and using the claimed method.

8. Claims 53, 78-82, 99 and 100 are rejected.

9. Claim 58 is objected to as being dependent upon a rejected base claim.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig
Examiner
Art Unit 1642

/Karen A Canella/
Primary Examiner, Art Unit 1643